

Susceptibility in Microbial Risk Assessment: Definitions and Research Needs

John Balbus, Rebecca Parkin, and Martha Embrey

Center for Risk Science and Public Health, The George Washington University School of Public Health and Health Services, Washington, DC, USA

Under the 1996 Amendments to the Safe Drinking Water Act (*1*), the U.S. Environmental Protection Agency (U.S. EPA) must consider susceptible subpopulations in its health risk assessments. The amendments mention specific groups, including young children, the elderly, pregnant women, and people who are immunocompromised by disease or treatment for diseases. The concept of susceptibility to adverse health outcomes from environmental exposures can be extended to other groups as well. For chemical exposures, a great deal of current research is the analysis of how differences in metabolic phenotypes modify the effects of toxic exposures. For microbial exposures, concepts of susceptibility have generally been limited to the permanent or transient protection from infection afforded by previous exposure. Little consideration has been given to the degree to which individuals may differ in the completeness of protection offered by their immune systems. In addition to genetic factors, nutritional status, systemic diseases, and toxic insult may alter the ability to mount an effective immune response. Social factors, such as access to health care, may also modify the course of infection with microbial pathogens.

Risk assessment is an inherently multidisciplinary process, and yet the disciplines needed to address technical issues in microbial risk assessment (e.g., secondary spread, virulence) are not applicable to chemical risk assessment. Addressing this issue in a fresh, scientifically rigorous manner requires the interaction of scientists who have experience in conducting risk assessments with experts in recognizing, studying, and treating infectious diseases. On 30 November and 1 December 1999, the George Washington University's Center for Risk Science and Public Health (Washington, DC) convened a workshop titled "Incorporating Susceptibility into Microbial Risk Assessment." The goal of this workshop was to produce a consensus document with multidisciplinary input that defined susceptibility to microbial pathogens for the purposes of risk assessment and which provided a framework for incorporating data on susceptibility into microbial risk assessments. The specific objectives were to *a*) create a group process that effectively involved multiple disciplines, including those not traditionally involved in risk assessment, such as pathology and immunology; *b*) clarify the conceptual elements of susceptibility for the purposes of microbial risk assessment; *c*)

identify the data sources for the elements of susceptibility in microbial risk assessment; and *d*) list the elements of susceptibility that need to be incorporated for different applications of microbial risk assessments.

Workshop Design

Individuals from a variety of disciplines were invited to the 2-day workshop. Represented disciplines and areas of expertise included infectious disease epidemiology, clinical infectious disease, molecular genetics, microbiology, laboratory practice, statistical modeling, toxicologic risk assessment, immunology, pathology, and environmental health of underserved populations. Because of the complexity of the subject, the workshop structure used the parallel efforts of three interdisciplinary breakout groups to address identical issues.

The workshop conveners devoted the morning of the first day to introductions and background presentations on approaches to susceptibility and microbial risk assessment. The first day's breakout session aimed to stimulate active exchange among disciplines in the context of specific scenarios of waterborne diseases. The second breakout session addressed the definition of susceptibility, and the third breakout session addressed data sources and research needs. The exact questions posed are shown in the appendix.

Background Presentations

The workshop conveners began by summarizing the definitions of susceptibility found in major dictionaries, relevant texts, interdisciplinary group reports, agency guidelines, and regulatory documents (*2*). Disciplines tend to define susceptibility in terms that fit their scientific orientations and methods. Disciplines such as medicine and biology are apt to frame susceptibility in individual terms, whereas toxicology and epidemiology are more likely to use a group perspective that more strongly emphasizes statistical concepts such as probability and variability. Three definitional components are shared among disciplines. Definitions of susceptibility consistently include a characterization of the host's physiologic state, a relationship between an agent and a host, and some outcome in the host that is caused by the agent. At the same time, definitions emphasize or add different aspects: some focus only on the host, whereas others qualify some aspect of the agent (e.g., dose or exposure levels), whereas some restrict outcomes to adverse

events, others compare the individual's (or subpopulation's) susceptibility to a population norm, and other definitions explicitly incorporate statistical concepts. It is not surprising that the definitions developed by interdisciplinary groups and found in agency guidelines often merge several concepts that reflect the disciplines of the participants in each process. Regulatory documents tend to focus on observable characteristics of subpopulations, such as age or exposure. Thus, there are diverse approaches to defining susceptibility, and any one of the numerous definitions of susceptibility may offer particular components for microbial risk assessment purposes.

After the presentation of different definitions of susceptibility, Balbus and Parkin (*3*) proposed a definition of susceptibility as a starting point for the breakout groups:

A set of identifiable traits within an individual or population that increases that person's or population's risk of an adverse health outcome as the result of specified environmental exposures.

Depending on the specific definition of susceptibility used in a microbial risk assessment, there are a number of ways in which the concepts of susceptibility can enter into a microbial risk assessment. Definitions that include a higher probability of exposure or a higher intensity of exposure may incorporate data on water consumption and usage, for example, into the exposure assessment phase of the risk-assessment paradigm. The substitution of distribution functions for individual point estimates of consumption allows interindividual differences in exposure to be explicitly incorporated. Alternatively, separate analyses could be employed using separate

Address correspondence to J. Balbus, Department of Environmental and Occupational Health, School of Public Health and Health Services, The George Washington University Medical Center, Warwick Building, Suite 201, 2300 K Street, N.W., Washington, DC 20037 USA. Telephone: (202) 994-1734. Fax: (202) 994-0011. E-mail: eohjmb@gwumc.edu

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ranges or distribution functions for specific subpopulations (e.g., children).

Addressing susceptibility in a dose–response analysis depends on the availability of data on different individuals or subpopulations, which is generally limited for this purpose. Incorporating susceptibility in this step of risk assessment will also depend on which dose–response function is selected; that is, which function is appropriate for the organism being considered. Epidemiologic parameters, such as case–mortality or case–morbidity ratios, may be useful for addressing subpopulation differences when there is a probability of serious health outcomes after infection.

A discussion of issues related to susceptibility should be included throughout the risk-assessment process, including the goals of the risk assessment, populations to be considered, assumptions made about exposure, dose response and other parameters, and characterization of residual uncertainties. Risk assessors should consult with experts in fields relevant to the susceptible populations being considered, such as pediatricians, gerontologists, and immunologists. In addition, stakeholder involvement is critical and needs to be structured in such a way as to include potential susceptible subpopulations.

Defining Susceptibility

Concepts of susceptibility. In discussions focused on developing a definition of susceptibility, the participants agreed that, for microbial risk assessment, *a*) susceptibility must be organism specific; *b*) outcomes considered for susceptibility need to be specific, carefully selected, and clearly defined; *c*) there are definitional elements that fit the two levels on which susceptibility could be defined (the individual and population levels); and *d*) factors that make up susceptibility do not by themselves constitute a definition of susceptibility.

The attendees also noted that an individual's risk of adverse health outcomes is dynamic and exposure or dose dependent. They discussed the changing probabilities of infection and the severity of health outcomes within individuals over their lifetimes. The participants agreed that susceptibility modifies the likelihood and/or severity of impact(s) of a specific exposure or external agent.

In their discussions to define susceptibility more clearly, the participants focused on the features that distinguish the two levels on which the term may be defined—the individual and the population scales (appendix). Although consensus was readily achieved on the individual scale, the population level proved more challenging. Some participants envisioned the aggregate scale from the individual perspective—that is, in terms of the

features of a collection of individuals. Some saw it as the combined result of host, agent, and behavioral characteristics (including secondary spread) across the population. Others conceived of it in more statistical or probabilistic terms. These differing views of the population scale of susceptibility were explored but not resolved into a consensus viewpoint during the workshop.

Definitional issues. Concerns raised in the workshop demonstrated that the participants were not in full agreement on a number of issues that may influence the final “best” definition of susceptibility for microbial risk assessments. The primary issues raised included *a*) whether a broad (public health) or narrow (medical) definition is more appropriate; *b*) whether population concepts should be included or excluded; *c*) whether intrinsic and extrinsic factors are nonmodifiable and modifiable, respectively; *d*) whether susceptibility exists in the absence of exposure or is conditional on exposure; *e*) whether pathogen characteristics should be included or excluded; *f*) whether probability of exposure should be included or not; *g*) whether dose should be included or eliminated; *h*) whether susceptibility is a modifier of the effect(s) caused by a specific exposure; and *i*) how outcome(s) should be defined (e.g., what should be considered “bad” and whether infection should be considered an outcome).

For example, the participants recognized that, particularly in the case of microbial pathogens, population characteristics affect the individual's probability of susceptibility and exposure. Secondary spread, infection, and herd immunity were noted as particularly important concepts to consider. Questions were raised about whether immunity should be seen as beneficial or not, whether duration of immunity should be addressed, who the true population at risk may be, and how that population could be readily identified. The group recognized that these issues would have to be answered on an organism-specific basis.

In addition, one breakout group noted that persons at high risk of adverse health outcomes are those who are highly likely to be either susceptible or exposed, or both. They concluded that high-risk populations are not made up of susceptible individuals alone. Given that legislative, regulatory, and policy documents seek to address subpopulations that are at high risk of being either susceptible and/or exposed, any definition of susceptibility for risk assessment may not necessarily address all people who need to be protected from adverse health events. One group pointed out that for the definition of susceptibility, scientists tend to exclude, whereas the public or nonscientists include, exposure characteristics. The workshop attendees recognized that there may be significant

legal and public health implications resulting from the definition of susceptibility. An important future step will be to conduct a sensitivity analysis of the effect of including exposure factors in the modeling of susceptibility versus not including them.

Proposed definition. After the reports to the full group, the three breakout groups individually reconsidered their definitions of susceptibility. In their final presentations, the “best” sense of the group about the definition of susceptibility was formulated:

Susceptibility is a capacity characterizable by a set of intrinsic and extrinsic factors that modify the impacts of a specific exposure upon risks/severity of outcomes in an individual or population.

However, discussions did not clarify whether, for the purposes of microbial risk assessment, “exposure” in the definition should be more specifically stated as “external agent” or “dose.” Also, “adverse” was not used to describe outcomes, and some participants felt that “or population” should not be included in the definition. These areas lacking consensus reflect the participants' diverse understandings of terms based on their different disciplines and professional experiences. The workshop attendees recognized that, although the scientific concept of susceptibility was originally defined on an individual basis, a broader population-scale approach incorporating identifiable factors might be more appropriate for microbial risk assessment.

Identifying Research Needs

During the last discussion scheduled on the workshop agenda, the charge to participants was to address the adequacy of current surveillance and research methods for providing data on susceptibility. The groups discussed questions on identifying and filling data gaps, needs and approaches for changing current data gathering systems, and strategies for validating risk assessment models.

Specific research studies. A major challenge to identifying and characterizing the subpopulation at increased risk from microbial exposure is that most studies (e.g., microbial challenge studies) use healthy adults as subjects and do not use people likely to be at increased risk, such as children or the immunocompromised. The participants offered a number of ideas for specific research studies that would examine the problem of defining susceptibility. The discussions frequently came back to the need for more information on endemic disease rates so that rates in a particular subgroup could be compared with a reliable background rate. These data could also be linked with risk factors such as drinking water consumption, drinking water source, and recreational water usage.

The participants suggested comparing illness rates in susceptible groups, such as immunocompromised people or the elderly, according to their drinking water source (e.g., pristine groundwater vs. contaminated surface water). These types of studies would characterize who gets sick and also help detect any possible waterborne link. Another suggestion was to prospectively follow people traveling to areas with high rates of endemic disease and characterize those who get ill and those who do not. Though it is less likely that people with immunocompromised conditions would travel to exotic or less developed places, the elderly traveler and possibly children could be studied. Also, different areas of the United States have varying rates of disease, so a study on the effect on visiting or moving to another region may be useful.

Conducting a case-control study on deaths or hospitalizations related to diarrheal disease may also shed light on susceptibilities and possibly water-related risk factors. A 1991 study reviewed death certificate data between 1979 and 1987 that listed diarrhea as a cause (4). Those at highest risk were not children, as one might expect, but elderly (> 74) females living in long-term care facilities. Similar studies emphasizing transmission risk factors (such as residence in a nursing home) could prove to be useful.

Traditionally, diarrhea has been the study outcome when investigating waterborne disease; however, there was some talk among the groups to expand the focus and consider other, less common measures of waterborne disease, such as quality-adjusted life years and disability-adjusted life years. Another suggestion was to study only severe adverse outcomes instead of just diarrhea (e.g., hospitalization, death). Such outcomes, some argued, would not only be more clinically significant, but also easier to find, document, and study in highly susceptible populations than diarrhea alone. In addition, discovering more impact on the population from waterborne disease could increase societal awareness and funding.

Because exposure and pathogenicity of the agent, as well as the susceptibility of the host, define population risk of waterborne disease, participants felt that basic research into pathogenesis and dose response would help determine who is susceptible to disease and why. Developing animal and *in vitro* models as surrogates for human exposure could increase the meager database on pathogen dose response (e.g., a swine model currently used for hepatitis E). It was also pointed out that the new information provided by advances in molecular biology, such as the Human Genome Project, will offer additional opportunities for characterizing the genetic bases of susceptibility.

Current surveillance systems. In the United States, waterborne disease outbreaks are tracked using voluntary passive surveillance techniques by the Centers for Disease Control and Prevention (CDC, Atlanta, GA) in collaboration with the U.S. EPA. State and local health departments may report the epidemiologic data from an outbreak to the CDC, but reporting varies by the type of outbreak, state, and time period. Such data often do not include the types of demographic or other individual characteristics essential for assessing interindividual differences in susceptibility. Exposure analysis is also limited and water quality parameters are not always included in the analysis.

The workshop participants' discussion of current surveillance systems centered on FoodNet (the Foodborne Disease Active Surveillance Network), under the joint administration of the CDC, the U.S. Department of Agriculture, and the Food and Drug Administration (5). FoodNet data are based on findings from 300 clinical laboratories within targeted geographic sites. All of the laboratories routinely test incoming stool samples for *Campylobacter*, *Salmonella*, and *Shigella*, but only some of them routinely test for other pathogens such as *Escherichia coli* O157:H7 and *Cryptosporidium*.

Participants suggested that FoodNet results might be used to help characterize susceptibility in the affected populations, even if the source of the infections was not necessarily water. Obviously, the pathogens of interest in the FoodNet program are those that are common causes of foodborne illness. Pathogens such as *Cryptosporidium* and *Shigella*, which are currently in the program, are both food- and waterborne; adding other pathogens to the surveillance effort that are also typically associated with water would add to the scarce information currently available on the occurrence of these pathogens and who is susceptible to them. Unfortunately, with the exception of some adenoviruses and Coxsackie viruses, the ability to detect pathogens in stools is limited to bacteria and, less efficiently, protozoa. Viruses, even those that are culturable, are rarely included as part of a clinical laboratory test protocol. Thus, this method of gaining insight into endemic waterborne disease is currently severely limited, and epidemiologic data are still required to detect and characterize viral outbreaks. As viral detection methods improve, this protocol could change.

The discussants also mentioned the PulseNet program (6). By comparing the fingerprints of bacterial strains isolated throughout the country, PulseNet identifies infections from the same strain that may indicate exposure to a common source, such as a contaminated food product. This is

especially important for foodborne outbreaks; one food processor can ship contaminated food all over the country in a matter of hours. To the extent that waterborne outbreaks are limited geographically, PulseNet may not be useful. Moreover, in most situations, contaminated water responsible for an outbreak will have long since reached the consumer, and interventions with drinking water may not be as effective as with food products. Exceptions to this would include products such as bottled water. In addition, similar fingerprinting techniques have been used in research settings to link microbial isolates from clinical samples with isolates from environmental samples, such as source water.

Surveillance needs. The workshop participants strongly emphasized the need to institute targeted, active surveillance and not just rely on the current passive surveillance system to collect information on susceptible populations. Toward that end, the group suggested different methods of using sentinel populations:

- Develop a longitudinal surveillance system using subjects who report weekly on their health status and supply periodic stool samples for analysis
- Study children with diarrhea; sample the stool of every tenth child presenting with diarrhea at targeted facilities to increase knowledge of endemic disease
- Reimplement family watch programs, which were used effectively during the 1960s and 1970s. In these studies, hundreds of families in New York and Seattle completed health diaries and provided periodic clinical samples such as blood. The results revealed important incidence and transmission data on a number of viral infections from adenovirus to influenza
- Recruit sentinel physicians to report regularly on possible waterborne illness (i.e., diarrheal disease)
- Recruit health maintenance organizations to serve a similar sentinel function.

An example of a local program that has instituted aggressive public health surveillance is in New York City (7). Officials have developed a waterborne disease risk assessment program that uses several methods of monitoring and surveillance. Active surveillance has been put in place for tracking cases of giardiasis and cryptosporidiosis. Methods include regular laboratory surveillance, follow up with physicians or patients for missing demographic information, and interviews with patients to determine risk factors. Reports from three separate sources make up their outbreak detection program. Distributors convey sales of over-the-counter antidiarrheal medications to pharmacies, and direct cash register sales from pharmacies are monitored weekly; three clinical laboratories report daily on the

number of stool samples they receive for testing; and 12 nursing homes fax reports of new cases of gastrointestinal disease in their 1,850 residents daily. This extensive monitoring program has generated important data on the incidence of cryptosporidiosis and giardiasis. The outbreak detection systems were instituted starting in 1995 and phased in through 1997. Although the results have been used to establish trends in the incidence of diarrheal disease in the New York metropolitan area, the program has not been fully used to analyze interindividual differences in risk factors.

Challenges to enlarging surveillance programs include a lack of time and money. Whereas almost all laboratories in the United Kingdom standardly test stool specimens for a variety of pathogens, ranging from *Campylobacter* to *E. coli* O157:H7, the economic disincentives inherent in the U.S. health system hinder such widespread testing.

States play an essential role in surveillance but frequently suffer from a lack of resources. Some states already use monetary incentives to encourage physician reporting. During the discussion, most contributors agreed that the use of the Internet might make reporting easier for physicians and laboratories at little to no additional cost. Some suggested tapping into geographic information systems technology to improve routine surveillance efforts and the ability to identify geographical and temporal illness clusters.

Another issue that participants stressed is the lack of collaboration between public health authorities and water utilities. Several group members noted that the utilities tend to focus on and are better equipped to study exposure-related factors, whereas public health authorities support health effects research. Providing the opportunities and proper incentives for collaboration between the two entities was viewed as crucial to

improving the quality of waterborne disease studies.

Large population-based health surveys could be another method of gathering data on drinking water exposure issues such as consumption patterns. Health information from the National Health and Nutrition Examination Survey (NHANES) (8) would be difficult to link to particular water sources because of the lack of geographic identifiers. It was noted, however, that it might be possible to add questions related to water consumption to NHANES in a given year, as it is now being modified more frequently. It may also be useful to archive blood samples from NHANES or other large surveys to research endemic disease rates as more sophisticated immunologic methods become available.

In summary, the workshop discussants concluded that significant gaps persist in understanding the population's susceptibility to microbial pathogens. Their consensus was

Appendix: Breakout Session Task Assignments

Breakout session 1: exploring scenarios. Within the context of the one given population and set of sources described below, each group was assigned only one of the hypothetical scenarios to address.

Population. A community of 1 million people; generally ethnically and racially diverse, also with a large subcommunity of immigrants from Southeast Asia; 15% of the population over age 70; 50% of households have children living at home, 15% of those households with children up to and including 2 years old; 2% of the population is HIV positive; there is a large army base on the outskirts of town.

Sources of ingested pathogen exposures. In this community, microbial pathogens are transmitted via drinking water supplied by surface water sources and may be transmitted by recreational water and water used to process foods. Seasonal flash floods occur in some years.

Scenarios

1. Clinical laboratory reports show an increase in positive *Giardia* samples following an elevated number of diarrhea cases.
2. Physicians notice an unusual number of non-AIDS patients presenting with *Mycobacterium avium* complex.
3. Two weeks after an enteroviral outbreak, physicians have detected > 200 new cases of acute cardiac disease.

Questions

1. What factors are important in measuring exposure to the microbe?
2. What factors are important in measuring the health outcome(s)?
3. What factors are critical to determine susceptibility in the population?

Breakout session 2: defining susceptibility.

Questions

1. What elements must be included in a definition of susceptibility?
2. What elements must be excluded?
3. What is your group's consensus definition of susceptibility?
4. Are there any aspects of susceptibility to ingested microbial pathogens and the range of health outcomes associated with them that would necessitate a change in this definition? If so, how

would your group change it for the purposes of microbial risk assessment?

Breakout session 3: identifying research needs.

Questions

1. What data and/or data systems are needed to advance knowledge about the U.S. population's susceptibility to microbial pathogens?
2. What would you change about current methods and systems to collect and record the needed data?
3. What strategies will be needed to validate microbial risk assessment models that incorporate susceptibility? What changes in policy and/or procedures will be needed to assure that sufficient data are available for validation efforts?

Features of Individual and Population-Level Definitions of Susceptibility

Individual level. A host's capacity to respond to an agent could be characterized by a set of intrinsic and extrinsic factors. Examples of intrinsic factors are genetic traits, age, and gender. Examples of extrinsic factors are access to health care and occupation. An individual's level of susceptibility is determined by the combined impacts of these factors.

Population level. Susceptibility deals with the probability or risk of adverse health outcomes associated with a specific exposure or dose. Examples of outcome are social burden of disease and severity of the outcomes. In a population, there is a distribution of individual probabilities of response at a given exposure level. Susceptibility at the population level may be characterized in different ways. For example, it may be described as *a*) individuals at the upper end of the spectrum of likelihood of suffering adverse health outcomes associated with the organism; *b*) individuals with identifiable characteristics or exposures that relate to the probability of adverse health outcomes and that serve as surrogates to measure risk in the population; *c*) the combined impact of intrinsic or acquired factors, characteristics of the pathogen of concern, and the probability of exposure to that pathogen; or *d*) a series of conditional probabilities including the probabilities of exposure, infection, disease (type and severity), and shedding of the organism.

that there are limited data on basic rates of endemic disease to determine differences in susceptibility within a population or subpopulation. Increased monitoring and the addition of active surveillance of waterborne disease and outbreaks would enhance the limited information obtainable from current passive surveillance systems. However, even if unlimited resources were available for such an expansion, the fragmented U.S. public health infrastructure would make it difficult to maintain a single nationwide surveillance system. An important step would be improving communication and collaboration between local and state health authorities and the water utilities regarding waterborne disease issues. There may be ways to enhance programs that are already in place, thereby increasing the ability to identify factors affecting susceptibility to microbial pathogens.

Conclusions

Although the participants acknowledged that a full consensus on how to define and incorporate susceptibility into microbial risk assessment was unlikely to emerge from a brief workshop, there was a positive sense of movement toward greater understanding of the interdisciplinary issues underlying microbial susceptibility. Many valuable suggestions were made for enhancing existing databases and developing studies that could more effectively reveal susceptible subpopulations' risks from microbial pathogens. Key conceptual issues included clarifying the distinction between individual- and population-scale definitions of susceptibility; identifying which intrinsic and extrinsic factors are modifiable and which

health outcomes should be considered adverse; determining whether susceptibility exists in the absence of exposure or is conditional on it; and determining whether agent, exposure, or dose should be included in a definition of susceptibility.

The participants agreed that there are a number of serious gaps that must be addressed before susceptibility can be adequately characterized. More studies that assess rates of endemic waterborne disease are needed, and these studies should analyze the effects of risk factors such as drinking and recreational water usage and individual demographic and health characteristics. Additional information on susceptibility may be gained by prospective studies of travelers to areas with high rates of endemic disease. Changes needed in U.S. surveillance systems include improved coordination of the currently fragmented public health infrastructure; more resources for targeted active surveillance of waterborne disease and outbreaks; and enhancement of existing population-based food and waterborne disease data systems. Research needs include more basic science research into pathogenesis and the development of animal and *in vitro* models for characterizing pathogenesis and dose response. Finally, public health authorities and water utilities are called on to improve their collaboration on waterborne disease issues.

The participants' high level of engagement in the workshop made clear the importance and timeliness of susceptibility as an issue in microbial risk assessment. Addressing the issues of susceptibility in a more rigorous manner and continuing this

multidisciplinary discussion will be critical to developing improved methods for microbial risk assessment.

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Workshop Leaders

Moderator

Lynn Goldman, Johns Hopkins University

Breakout Group Chairs

Henry Bradford, Jr.
Louisiana State Department of Health and Hospitals

Gunther Craun
Gunther F. Craun and Associates

Howard Kipen
University of Medicine and Dentistry of New Jersey